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Catalytic Regioselective Oxidation of Glycosides**

Manuel Jäger, Marcel Hartmann, Johannes G. de Vries,* and Adriaan J. Minnaard*

Currently, functional group transformations on carbohydrates are highly reliant on the use of protecting groups. These protecting groups serve different functions, 1) to protect all hydroxy groups except one to allow selective modification, including glycosidic bond formation, of the remaining hydroxy group,^[1] 2) to steer the reactivity at the anomeric center by stabilizing or destabilizing the incipient oxonium ion (arming, disarming)^[2,3] and to allow stereoselective glycosidic bond formation through anchimeric assistance (neighboring group participation),^[4] 3) to allow solubility of carbohydrates in nonpolar organic solvents and purification by silica gel chromatography. As a consequence, the preparation of a desired carbohydrate, even a straightforward derivative of a commercially available monosaccharide, frequently requires a multistep route comprising protection and deprotection steps. The selective modification, in particular oxidation, of hydroxy groups in unprotected carbohydrates is therefore highly desired. At least, it would remedy the necessity to balance the protecting-group strategies for protection and glycosidic bond formation.

Nevertheless, the selective oxidation of carbohydrates, of which pyranosides are the most important representatives, is a longstanding challenge in organic chemistry. The selective oxidation of the primary hydroxy group in pyranosides, chemically by using the 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO)^[5] or enzymatically by uridine 5'-diphosphoglucose dehydrogenase,^[6] has been well-described. In contrast, the selective oxidation, or even conversion in general, of the secondary hydroxy groups is extremely difficult and barely known.^[7] Tsuda et al. have described the selective oxidation of several methyl glycosides with stoichiometric dibutyltin oxide and bromine.^[8,9] Although good yields were obtained and the regioselectivity could be steered

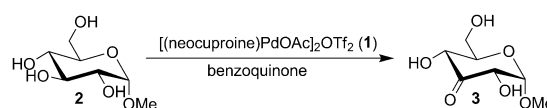
by choice of the substrate, the use of stoichiometric amounts of organotin reagents limits the use of this approach.

The enzymatic oxidation of several carbohydrates, including glycosides, has been described by Köpper and co-workers.^[10] By using pyranose oxidase, selective oxidation at C2 and C3 was achieved, depending on the substrate. For reducing carbohydrates, the yields were generally high, but for glycosides low yields were observed. The activity of this enzyme is rather low. This and the substrates being restricted to the β -anomer, have prohibited the application of this method. Another enzymatic approach has been described by Haltrich et al. in which a fungal pyranose dehydrogenase was able to oxidize a series of carbohydrates on C1, C2, C3, C1,3', or C2,3'.^[11,12] However, yields of isolated products were not reported.

We describe here the first catalytic, regioselective oxidation of unprotected pyranosyl glycosides, both mono- and disaccharides, to the corresponding ketosaccharides. Given the wide scope and high selectivity of the reaction, this approach is a significant step towards protecting-group-free carbohydrate synthesis.

Inspiration was obtained from recent work of Waymouth and co-workers on the palladium-catalyzed oxidation of glycerol to dihydroxy acetone.^[13] Their cationic 2,9-dimethylphenanthroline (neocuproine) palladium complex selectively oxidizes the secondary hydroxy group with excellent selectivity and yield. We wondered whether this approach would also be able to discriminate between multiple secondary hydroxy groups. This would then possibly provide a catalytic method for the oxidation of unprotected carbohydrates to their corresponding keto sugars.

We commenced to study this hypothesis by treating methyl α -D-glucopyranoside (**2**) with catalyst **1** (2.5 mol %) in aqueous acetonitrile by using benzoquinone as the terminal oxidant (Scheme 1). ¹H NMR and IR spectroscopy indicated



Scheme 1. Selective oxidation of methyl α -D-glucopyranoside.

the formation of a single oxidation product within 3 h. After isolation (see below) and thorough 2D-NMR studies, this product turned out to be **3**.

The use of DMSO as the solvent considerably accelerated the reaction and this encouraged the further optimization of the catalyst system. The use of dichlorobenzoquinone (DCBQ) instead of benzoquinone (BQ) led to a faster reaction, but required a minimum catalyst loading of

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1.1 mol% to reach full conversion. With benzoquinone, 0.5 mol% already sufficed. The use of oxygen as the oxidant resulted in a slower reaction and even 2.5 mol% of catalyst was not enough to reach full conversion after 48 h.

Initially, isolation of the product was problematic because of its polarity and supposed acid and base sensitivity. When the reaction was carried out in aqueous acetonitrile, it turned out that **3** could be isolated pure and in 96% yield by successive washings with ether and toluene, followed by evaporation of the residual water. In case the reactions were carried out in DMSO, percolation of the entire mixture over a charcoal column with water as the eluent removed the majority of this solvent, and subsequent chromatography on silica gel by using a mixture of CH₂Cl₂/acetone/methanol/water provided the pure product.^[14]

With the catalyst system and product isolation established, the scope of the reaction was studied. By using the same conditions, both methyl β-D-glucopyranoside (Table 1, entry 2) and methyl *N*-acetylamino-α-D-glycoside (entry 3) were selectively oxidized in 85% and 89% yield after isolation, respectively. Glucose and sorbitol were unselectively oxidized.

Methyl-2-α-D-desoxyglucopyranoside (Table 1, entry 4) was selectively oxidized using dioxane/DMSO (4:1) as a solvent and the product could be isolated in 60% yield. The anomeric phenyl-protected glycoside **10** (Table 1, entry 5) was also cleanly oxidized to **11**, which was isolated in 73% yield.

Oxidation of thiophenyl glucopyranoside **12** gave **13** in a clean reaction, but the product was isolated in only 47% yield. Here 6.5 mol% of catalyst had to be used to drive the reaction to completion.

Subsequently, the influence of the primary hydroxy group on the reaction was studied, since we suspected its involvement in the stereoselectivity. The *tert*-butyldimethylsilyl substituent in **14** was completely removed during the reaction^[15] and the expected product was isolated in good yield. The less-sensitive *tert*-butyldiphenylsilyl substituent in **15** withstood the reaction conditions, and in DMSO (which was used because **15** did not dissolve in acetonitrile) oxidation was complete in 15 min affording **16** in 66% yield. Furthermore, benzoyl-substituted **17** was cleanly oxidized as well, though product **18** was isolated in a decreased 45% yield. Apparently neither the presence nor the nature, electron-donating or -withdrawing, of the substituent has an influence on the selectivity of the reaction.

Although the formation of small amounts of regioisomeric products cannot be excluded, the variation in yield (Table 1) is not due to a lack of selectivity of the reaction, because the NMR spectra of the crude mixtures show oxidation solely at C3 or at least with a selectivity of > 90% (see the Supporting Information). However, purification of these very polar compounds by flash chromatography diminished the yields.

To take our strategy a step further, we studied the selective oxidation of methyl maltoside **19** and methyl cellobioside **21**, as representatives of disaccharides containing an α- and β-glycosidic linkage (Scheme 2). Being able to selectively oxidize one hydroxy group in more-complex

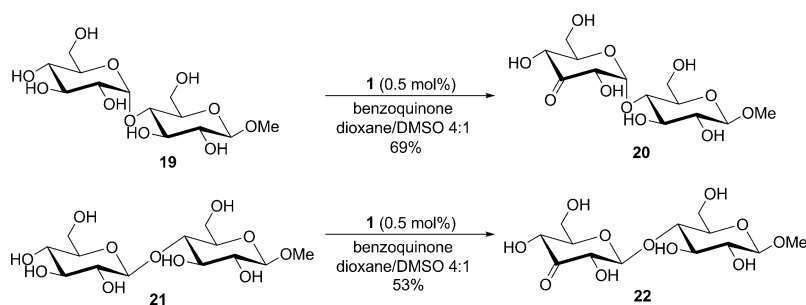
Table 1: The selective catalytic oxidation of monosaccharides.

Entry	Substrate	Product	Method ^[a]	Yield [%] ^[b]
1			A	96
2			A	85
3			A	89
4			B	60
5 ^[c]			B	73
6			C	47
7 ^[d]			A	96
8			D	66
9			D	45

[a] Method A: pyranoside (4 mmol), **1** (2.5 mol%), DCBQ (3 equiv), MeCN/H₂O 10:1, 0.3 M. Method B: pyranoside (0.8 mmol), **1** (2.5 mol%), DCBQ (3 equiv), dioxane/DMSO 4:1, 0.3 M. Method C: pyranoside (0.8 mmol), **1** (6.5 mol%) added in portions, DCBQ (3 equiv), dioxane/DMSO 4:1, 0.3 M. Method D: pyranoside (0.8 mmol), **1** (2.5 mol%), DCBQ (3 equiv), DMSO, 0.3 M. [b] Yields of isolated products. [c] **10** (0.4 mmol). [d] The TBS group was cleaved under the reaction conditions. TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

saccharides opens a multitude of opportunities to modify and access naturally occurring saccharides without the construction of glycosidic bonds. Also in these cases the reaction turned out to be highly regioselective, providing **20** and **22** in good yields after isolation. The identity of the products was established by COSY-, HSQC-, and NOESY-NMR spectroscopy.

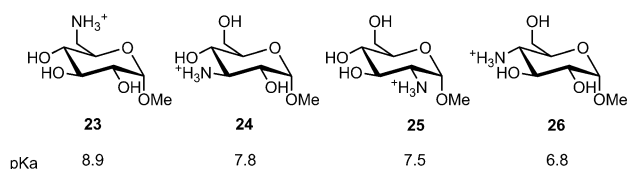
The observed preference of the catalyst to selectively oxidize the C3 OH group, also in connection with its substrate scope, is intriguing and currently cannot be fully explained. The stereochemistry at the anomeric center C1 (Table 1, entries 1, 2, and 6) and the nature of the substituent (entries 5 and 6) is apparently not relevant for the reaction outcome. Also the C2 OH group is not important, since it can be



Scheme 2. Selective oxidation of methyl β -D-maltoside and methyl β -D-cellobioside.

omitted (Table 1, entry 4) or replaced by an acetamido substituent (entry 3). Methyl α -mannopyranoside and methyl α -galactopyranoside, with axial C2 OH and axial C4 OH functional groups, respectively, are however not selectively oxidized. The primary C6 OH group stays consequently untouched, in line with the selective oxidation of glycerol, thereby making this method complementary to the aforementioned TEMPO-catalyzed oxidation.^[5] Substitution does not influence the selectivity of the oxidation.

A possible rationale for the regioselectivity could be a kinetically controlled coordination of the catalyst to the C3 OH group, followed by deprotonation and subsequent hydride abstraction. Whether simultaneous coordination to the C4 OH group assists in this process is not clear; it would explain the selective oxidation of the disaccharides **19** and **21** on the left residue, but steric hindrance could cause the same effect. The hypothesis derives some support from a study by Bols and co-workers.^[16] Comparing pK_a values in a series of methyl glucosamines **23–26** (Scheme 3), the C3 NH_2 turned



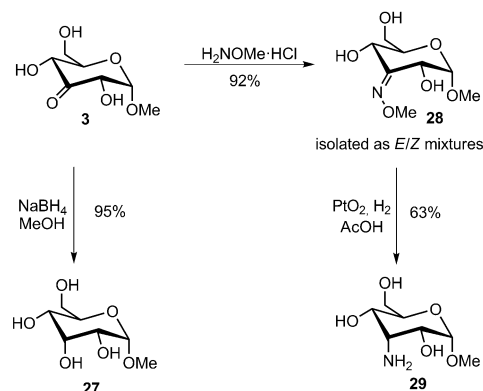
Scheme 3. pK_a values in a series of methyl glucosamines **23–26**.

out to have the highest pK_a value, which is an indication for a higher basicity/nucleophilicity of the corresponding C3 OH group.

A different study by Thiem and Matwiejuk, investigating the influence of partial protection on the pK_a value of the residual free hydroxy groups of methyl glycosides, shows that the isolated C4 OH group should be more basic/nucleophilic than the C3 OH group.^[17] Nevertheless it also shows that an increasing number of free vicinal hydroxy groups increases the acidity of the glycoside, probably because of intramolecular hydrogen bonding. If the C3 and C6 hydroxy groups are not protected, however, the basicity/nucleophilicity of the C3 OH group is even higher compared to the glycoside with only one free hydroxy group. Furthermore it has been shown by Li and Kalikanda that partial protection can lead to inversion of the reactivity of glycosides.^[18] Therefore an estimation of the

nucleophilicity of single hydroxy groups in glycosides remains difficult.

As a first demonstration of the synthetic versatility of the current strategy, protecting-group-free^[19] syntheses of methyl α -D-allose and methyl 3-amino-3-deoxy- α -D-allose (3-epi-kanosamine) were established. Allose is a rare monosaccharide, and currently prepared in four to five steps.^[20,21] Reduction of **3** with $NaBH_4$ in methanol^[22] leads directly to methyl allose in 95 % yield (Scheme 4).



Scheme 4. Synthesis of methyl α -D-allose and methyl 3-epi-kanosamine

Alternatively, **3** is converted into its corresponding *O*-methyl oxime **28** and subsequently reduced with H_2 /Adam's catalyst^[23] to afford methyl 3-epi-kanosamine **29** in 58 % overall yield as a single isomer, after peracylation to facilitate isolation.

In conclusion, the possibility to perform protecting-group-free synthetic transformations on carbohydrates has been brought a step closer by developing a Pd-catalyzed regioselective oxidation of pyranosyl glycosides. The applied Pd/neocuproine catalyst distinguishes between the various secondary hydroxy groups and selectively oxidizes the one at C3. A catalyst loading of 0.5 mol % (1 mol % Pd) is sufficient for full conversion on gram scale within hours at room temperature. The products are isolated in high yields, and the substrate scope is considerable, including both mono- and disaccharides. The selective oxidation of more-complex tri- and oligosaccharides is currently studied, and the approach could assist in the preparation of building blocks for automated carbohydrate synthesis.^[24] Although the origin of the regioselectivity is under study as well, kinetic product formation seems to be the most likely explanation. Application of the methodology is illustrated by the efficient synthesis of methyl allose and methyl 3-epi-kanosamine in high yield from methyl glucose.

Experimental Section

Methyl- α -D-ribo-hexapyranoside-3-ulose (**3**): Methyl- α -glucopyranoside (777 mg, 4.0 mmol, 1.0 equiv) and 2,6-dichloro-1,4-benzoquinone

(2.12 g, 12.0 mmol, 3.0 equiv) were suspended in acetonitrile/water (13 mL, 10:1, 0.3 M in substrate). The catalyst [(2,9-dimethyl-1,10-phenanthroline)-Pd(μ -OAc)]₂(OTf)₂ (105 mg, 2.5 mol %) was added, and the mixture was stirred at room temperature for 3 h. Toluene (50 mL) was added, and the mixture was extracted twice with water (7 mL). The combined water layers were washed once with ethyl ether (35 mL), filtered, and concentrated in vacuo to give the pure methyl- α -D-ribo-hexapyranosid-3-ulose (751 mg, 3.9 mmol) in 96 % yield as a dark brown solid. ¹H NMR (400 MHz, 298 K, [D₆]DMSO): δ = 4.95 (d, J = 4.2 Hz, 1H), 4.29 (dd, J = 4.2, 1.5 Hz, 1H), 4.07 (dd, J = 9.8, 1.4 Hz, 1H), 3.69 (dd, J = 11.9, 1.9 Hz, 1H), 3.59 (dd, J = 11.9, 4.9 Hz, 1H), 3.46 (ddd, J = 9.7, 4.9, 1.8 Hz, 1H), 3.26 (s, 3H). ¹³C NMR (50 MHz, [D₆]DMSO): δ = 206.1, 102.2, 75.4, 74.6, 71.9, 60.7, 54.4. HRMS (ESI): m/z : calcd for C₇H₁₂O₆Na ([M + Na⁺]): 215.053, found: 215.052; IR ν_{max} = 3436 (OH), 2947 (C–H), 1736 (C=O), 1031 (C–O) cm^{−1}.

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